the number of stress cycles is large enough. Fatigue is a major cause of failure in machinery; however there is no comprehensive theory of fatigue. To design machines, engineers use heuristic methods such as the Palmgren-Miner rule or S-N diagrams. Here, we investigate for the first time a molecular theory of fatigue failure. We aim to provide a theoretical basis for the heuristic methods engineers use to avoid fatigue failure and draw conclusions about the design of molecular machines such as kinesin or myosin motors.

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Mechanochemistry of Small Molecules: Into Which Bond does the Force Go?

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Regulation of (Bio)chemical reactions by mechanical force has been proposed to be fundamental to cellular functions[1]. Atomic force microscopy and molecular force probe experiments suggested an enhancement on the reactivity of thiol/disulfide exchange[2] and ring-opening of cyclobutene[3], respectively. Recently, we have performed hybrid quantum mechanical molecular mechanical simulations in combination with transition path sampling on the thiol/disulfide exchange. We could show that stretching a molecule can significantly shift the transition state, and also affects degrees of freedoms other than sole bond stretching [4].

In order to understand into which degrees of freedom the force goes, we have developed a force distribution analysis method for ab initio simulations, a simple scheme to deduce pairwise forces from non-pairwise quantum mechanical descriptions, which is transferable to any other (bio)chemical molecule for which internal stresses are of interest. The application to the ring-opening of cyclobutene shows how mechanical stretching forces propagate into the bonds of the reactive system, leading to both compressive and tensile forces in the strained cyclobutene. The force distribution allows to directly relate internal forces in bonds to mechanochemical events of bond scission.

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QM/MM Molecular Dynamics Methods Applied to Investigate Cellulose Fibers Hydration

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The imminent lack of fuel instigated by the upcoming end of the world's oil reserves has increased the interest in new energy sources. Biofuels are an alternative largely used in Brazil, where gasoline and ethanol consumption are about the same. However, to the ethanol production, just the sugarcane juice is employed and a large amount of biomass is not efficiently used. This colossal amount of resources, specially the cellulose fibers, is the basis to the production of the so called second generation biofuels.

Nevertheless, the crystalline structure of the cellulose fibers is a big challenge, since enzymes do not efficiently degrade this kind of structure, however they do efficiently break down imperfect fibers. Structural studies had shown the importance of a hydrogen bond web to stabilize these fibers. In this work, we are studying the behavior of this fiber using molecular modeling tools, in order to develop a technic to break down these hydrogen bonds, which should lead to the production of single chains or even a less structured fiber.

In this work, QM/MM MD simulations of a fully hydrated cellulose fiber segment were carried out to observe the influence of the hydration in the fiber stability. The structure obtained using these simulations were used as input in a DFT study of a small portion of the fiber. These QM simulations were carried out to study the energy and frequency of the inter-chain hydrogen bond. Our simulations are showing a very stable frequency value to these bonds and we could use it to break these H-bonds using QM/MM calculations, to produce a resonance phenomenon.

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Structural Thermodynamics of NMDA Receptor Ligand-Binding Domains

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Neuronal signaling is based on the release and detection of glutamate within the synaptic cleft. Regulation of this signaling has implications in both learning and memory, while dysfunction is implicated in a variety of neurological disorders, including Parkinson's and Huntington's diseases. Glutamate in the synaptic cleft is detected by glutamate receptors (GluRs), which are ligand-gated ion channels. N-methyl-D-aspartate receptors (NMDARs) are a class of GluRs that require the binding of both glycine and glutamate for receptor activation. Here, the free energy landscapes governing large-scale conformational transitions in the isolated ligand-binding domains (LDBs) of the NMDAR subunits NR1, NR2A, and NR3A are computed for both apo and holo forms using umbrella sampling simulations. The effects of both agonist insertion and amino acid substitutions on conformational stabilities in the various LBDs are examined.

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Ligand-Protein Interaction Studied by Computer Simulation and Time-Resolved X-Ray Crystallography

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Recently, high resolution x-ray crystallography demonstrated breathing motion of internal cavities in concert with ligand migration in myoglobin(Mb) [1]. Continuous pulsed illumination of carbomonoxy-Mb crystals at low temperatures has illustrated structural changes around each cavity in response to ligand migration. In the present study, we examined the effect of the breathing motion on the potential of mean force(PMF) for ligand-protein interactions by using molecular dynamics simulation and experimental derived from the x-ray study[1]. Conformational sampling of Mb was performed by NPT molecular dynamics simulation for 92 ns. We introduced three-dimensional lattice of regularly spaced grid points, and evaluated PMF at each point by the implicit ligand sampling method [2]. The effect of the breathing motion of Mb on the ligand-protein interaction was illustrated by the difference map of PMFs for Mb structures before and after light illumination. Our results show ligand escaping mechanism via Xe1 pocket and gate opening between Xe2 pocket and Xe3 pocket.

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3731-Pos Board B592

Molecular Dynamics Studies of Protein Targets for Cancer

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In this meeting, we present the molecular dynamics studies of two protein targets for cancers. The one is epiregulin (EPR), which is a member of the epidermal growth factor family and a factor affecting pancreatic cancer. Recently, it was observed that the binding affinity of EPR without S-S bonds for an antibody is lower than that of EPR with S-S bonds, and that the affinity of a long form type (extracellular domain) of EPR without S-S bonds is higher than that of a mature type without S-S bonds. To investigate the effect of the S-S bonds on the structural stability of EPR, we have performed molecular dynamics (MD) simulation for these three types of EPR. From our simulations, it has found that the S-S bonds reduce the structural fluctuation of EPR, and the structure of the mature domain in the long form type is similar to the mature type with S-S bonds. The other protein target is the loop region between fibronectin type III domains of roundabout-1 that is a receptor for Slit1 and Slit2 in axon growth cones and differentially expressed in cancers. We have investigated the structural stability and thermodynamic property of the loop region using MD simulation. We have calculated two types of peptide of different size: the peptide composed of 26 amino acid residues corresponding to the full region of the fluctuating loop, and the shorter one of 20 amino acid residues. In the 20 amino acid peptide calculations, we have observed two different stable conformations, which are stable during more than 1.5 μs. We have found that for the one conformation, the intramolecular interaction energy contributes to the thermodynamical stability, while for the other one, water binding to the turn part of the peptide is dominant contribution.

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Accelerated Molecular Dynamics Simulations of Thrombin-Thrombomodulin Reveal Potential for Entropic Allostery

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The specificity of the serine protease thrombin is altered from procoagulative cleavage of fibrinogen to anticoagulative cleavage of protein C upon distal binding of cofactor thrombomodulin (TM). The fourth EGF-like domain of TM (TM4) is necessary to elicit this response, though it makes no direct contact with thrombin. While this effect can be described as allosteric, crystal structures of apo and TM bound thrombin do not reveal a significant structural change, making a significant enthalpic contribution to allostery unlikely. We